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Additive-Free Green Light-Induced Ligation Using BODIPY Triggers

Ming Li,[c] Andrew P. Dove[b] and Vinh X. Truong*[a]

Abstract: Photochemical ligation is important in biomaterials engineering for spatiotemporal control of biochemical processes. Such reactions however generally require activation by high energy UV or short wavelength blue light, which can limit their use as a consequence of the potential of these high energy light sources to damage living cells. Herein, we present an additive-free, biocompatible, chemical ligation triggered by mild visible light. BODIPY dyes with a pendant thioether attached at the *meso*-position undergo photolysis of the [C-S] bond under green light (λ = 530 nm) excitation, producing an ion pair intermediate that can react specifically with a propiolate group. The utility of this photochemical ligation in materials science is demonstrated by the fabrication of hydrogels with specific architectures, photo-immobilization of biomacromolecules, and live cell encapsulation within a hydrogel scaffold.

Photochemical transformations were first performed using solar energy as the natural light sources.[1] With the development of lamp technology, chemists have had access to UV light with wavelengths as low as 200 nm and photon energy that is greater than that attained from sunlight.[2] This has allowed a wider range of photochemical reactions to be accessed. Nevertheless, reliance on UV light for activation of chemical processes significantly hinders their application in biomaterials science as a consequence of the high cost of equipment and energy usage, large heat generation and harmful side effects from UV light exposure.[3] Thus, new photochemical reactions that can be triggered by low energy, long wavelength visible light will significantly expand the applications of photochemistry in organic synthesis and materials engineering.[3] Furthermore, employment of red-shifted photoreactive moieties that avoids the use of damaging UV light and additives can further enable their utility in sensitive biological environments.[4] Perhaps more importantly, longer-wavelength absorption leads to deeper tissue penetration thus enhancing the translatability of this method.

Despite this need, reports that are focussed on catalyst free photo-ligation still mostly rely on the activation by short wavelength blue light (λ = 405-460 nm). In particular, Barner-Kowollik and co-workers reported visible light triggered ligation of polymers using 1,3-dipole 2H-azirine ligation (λ_{max} = 405 nm),[5] nitrile imine-mediated tetrazole-ene cycloaddition (λ_{max} = 405 nm),[6] and photoreversible styrylpyrene dimerization (λ_{max} = 420 nm).[7] The group of Zhu has extensively utilised coumarin derivatives as photocaging groups for construction of hydrogels via photo-uncaging of thiocarbamate (λ = 405-450 nm) followed by thiol-maleimide addition,[8] while An *et. al.* have reported several tetrazoles derivatives that can be activated by 405 nm laser light to generate nitrile imine for 1,3 dipolar cycloaddition.[9] More recently, Li *et al.* introduce a visible light-triggered [4+2] cycloaddition based on 9,10-phenanthrenequinone functionality that is activated at λ = 405-460 nm.[10] Our group has employed a number of visible light triggered photo-reactions, including photocycloaddition of anthracene[11] and styrylpyrene,[12] triggered by irradiation at λ_{max} = 420 nm, in the fabrication of dynamic hydrogels as biomaterials. Nevertheless, the short wavelength (λ = 405-455 nm) at which all of these chemistries operate, despite being non-harmful to living cells at low intensity,[13] is limiting their further application in biomaterials engineering due to the low tissue penetration property.

Recent computational studies by Winter and co-workers suggested that boron-dipyrromethene (BODIPY) moieties, in their excited state, can effectively decay, with the scission of [C-O] bond at the *meso*-position, to ground state ion pairs.[14] This theoretical analysis was practically confirmed by the caging and light-activated release of various groups including carboxylic acids,[14] amines,[15] and chloride[14a] under green light (λ_{max} = 520 nm) irradiation using BODIPY scaffolds. These advances inspired us to examine the possibility of using BODIPY in photochemical ligation by photo-induced scission of [C-S] bond to generate a short-lived thiolate anion that can be captured by an appropriate electrophile. Herein, we demonstrate that green light can be used to induce a nucleophilic thiol-yne addition by utilizing BODIPY scaffolds as the photo-trigger. BODIPY groups are used to directly cage the thiol group *via* a thioether linkage. Under irradiation of visible light at λ_{max} = 530 nm, the excited BODIPY-thioether is converted to an ion-pair intermediate which can participate in the nucleophilic thiol-yne addition (**Figure 1a**). Compared to the normal approach in which the caged-thiol is released from the thiocarbonate group,[8] here we take advantage of the high reactivity of the propiolate group towards the thiol anion. Critically, the thioether group is stable under ambient light in the absence of an electrophile, which is highly advantageous for storage and processing of materials prior to green-light-activated ligation.

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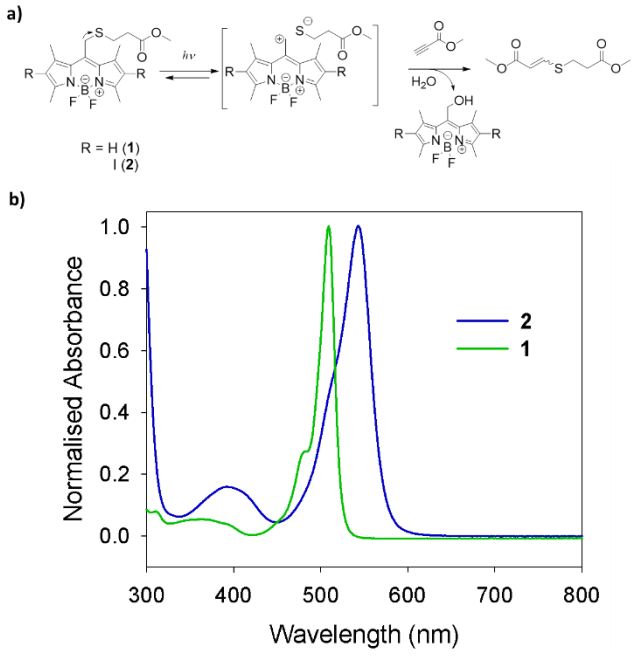

Figure 1. a) Mechanism of visible light activation of nucleophilic thiol-yne; b) UV-vis spectra of 1 and 2 in acetonitrile/water (v/v = 4/1).

The synthesis of BODIPY thioethers **1** and **2** was targeted to create a versatile precursor for photoligation (**Figure 1a**). The molecular design of these photocaged thiols was undertaken such that the ester group imparts significant versatility with which to attach a range of functional groups. Initially, we attempted to synthesise **1** *via* nucleophilic thiol-bromo addition (**Scheme S1**), however significant degradation of the BODIPY-Br was observed under several reaction conditions, even in the presence of a mild base such as triethylamine. Thus we re-examined the synthesis and prepared BODIPY from an acyl precursor that contains a thioether moiety (**Scheme S2**). This synthetic route resulted in the desired compound **1** with moderate yield (*ca*. 24%). Compound **2** can be synthesised from reaction of **1** with iodine monochloride in dichloromethane in good yield. As anticipated, UV-Vis spectra of compounds **1** and **2** in acetonitrile/water mixture show absorbance in the green light region (λ = 470-580 nm) with very high molar extinction coefficients (values of 68 000 M^{-1} cm^{-1} and 57 000 M^{-1} cm^{-1} for **1** and **2** respectively, see Table 1).

Table 1. Optical properties of **1** and **2** and quantum efficiencies of the conversion to alkene thioether.

Compound	λ_{max} (nm)	ε (x10^4 M^{-1} cm^{-1})	Φ[a] (x10^{-4})	εΦ (M^{-1} cm^{-1})
1	510	6.8	7.2	49
2	543	5.7	31	177

[a] Quantum efficiency of the conversion of BODIPY thioether to alkene thioether determined by ferrioxalate actinometry in water/acetonitrile at λ = 530 using a LED light source (I = 30 mW cm^{-2}) and the conversion was determined by ^{1}H NMR.

We next investigated the photochemical reactivity of the synthesised chromophores with methyl propiolate in water/acetonitrile (v/v = 1/4) under irradiation of green light at λ = 530 nm and intensity of 30 mW cm^{-2}. Inspection of the ^{1}H NMR spectra of the lyophilised products post-irradiation reveals the formation of the alkenyl adducts (**Figure 2 and S23**) similar to those observed from base-catalysed thiol-propiolate addition. The reaction did not proceed in chloroform (**Figure S16**), hexane or acetonitrile, even in the presence of the triethylamine which is a good catalyst for the nucleophilic thiol-yne addition (**Figure S17**). This suggests that polar protic solvents play a key role in this photochemical addition, presumably through stabilization of the ion-pair intermediate. Further analysis of the chemical shifts of the photoderived-adducts from either **1** or **2** with methyl propiolate reveals that the thio-alkene adduct is mostly *cis* isomer (88%). The predominant *cis* isomer adduct is similar to what was observed in the base-catalysed thiol-yne reaction in polar solvents.[16] Our photo-induced thiol-yne reaction however does not require a base catalyst, which presents a significant advantage with regards to the versatility of this reaction in a range of environments, including biological environments. Green light irradiation of both **1** and **2** in the absence of methyl propiolate in water/acetonitrile however, showed no reaction, which suggests that the thioether BODIPY compounds are stable to photo-induced hydrolysis.

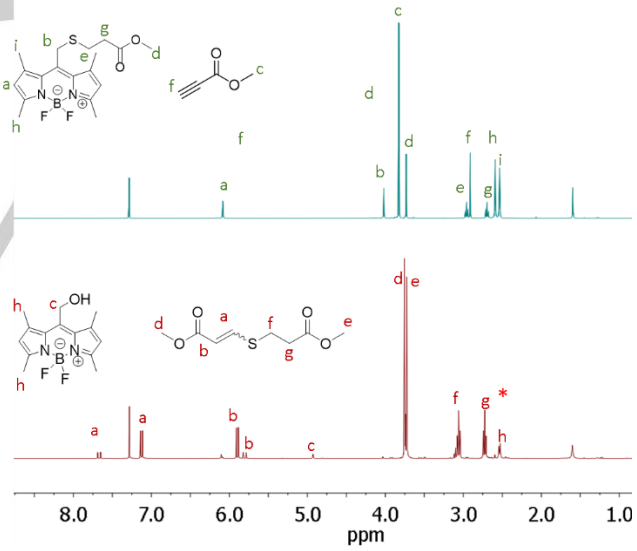

Figure 2. ^{1}H NMR spectra of compound **1** (1 eq.) and methyl propiolate (3 eq.). in water/acetonitrile (v/v = 1/4) before (**top**) and after irradiation (**bottom**) with green light (λ = 530 nm, I = 30 mW cm^{-2}) for 5 h. After irradiation, the solutions were lyophilised, during which methyl propiolate was evaporated together with the solvent, before being dissolved in $CDCl_3$ for NMR analysis.

As a consequence of the very low solubility of both **1** and **2** in both water and methanol, we were not able to monitor the reaction using HPLC. Thus the conversion of the BODIPY thioether to alkene thioether adduct was followed by ^{1}H NMR spectroscopy. After 2 h of green light irradiation, 43% of **1** was consumed in the photo-induced reaction with methyl propiolate,

while 81% of **2** was consumed under the same reaction conditions (**Figure S21**). Clearly, the iodinated derivative **2** not only showed a redshifted absorbance but also a higher chemical quantum efficiency in the photo-triggered thiol-yne addition. This may be a result of the intersystem crossing to a triplet state being enhanced by the iodine atoms, which have a longer lifetime compared to the singlet states under excitation,[14b] This consequently increases the stabilization of the ion-pair intermediate for nucleophilic conjugation.

In tracking the photochemical addition process, we were able to isolate the alcohol by-products using preparative thin layer chromatography (**Figure S27**-**S30**). The chemical structures of the alcohol by-products were confirmed by ^{1}H NMR spectroscopy and high resolution mass spectrometry (HRMS), confirming the mechanism of the photoligation shown in **Figure 1**. Furthermore, performing the light-induced reactions in degassed solutions and under argon protection showed no difference in the conversion compared to untreated solvents and under ambient atmosphere, suggestive of minimal interference from oxidation by singlet oxygen generation.[17]

To demonstrate the versatility of this approach, we also examined the photochemical ligation of the thioether BODIPY with common nucleophiles including acrylate ester and maleimide. Irradiation of **1** or **2** and methyl acrylate in acetonitrile/water with green light after 5 h did not result in any observable thiol-ene addition product. This result indicates that the acrylate group is not a strong enough electrophile for reacting with the ion pair intermediate. Irradiation of **1** or **2** with *N*-ethylmaleimide led to a number of by-products accompanied by photobleaching (**Figure S22**). We were not able to identify the thiol-maleimide or alcohol product (BODIPY-OH) when analysing the resultant solution by HRMS. A reasonable explanation for this is that the maleimide acts as an electron acceptor for the donor-excited photoinduced electron transfer (d-PeT) effect, following the excitation of the BODIPY moiety (**Figure S23**).[18] Consequently, the activated maleimide underwent oxidation and hydrolysis in aqueous media, resulting in an array of unidentified products.

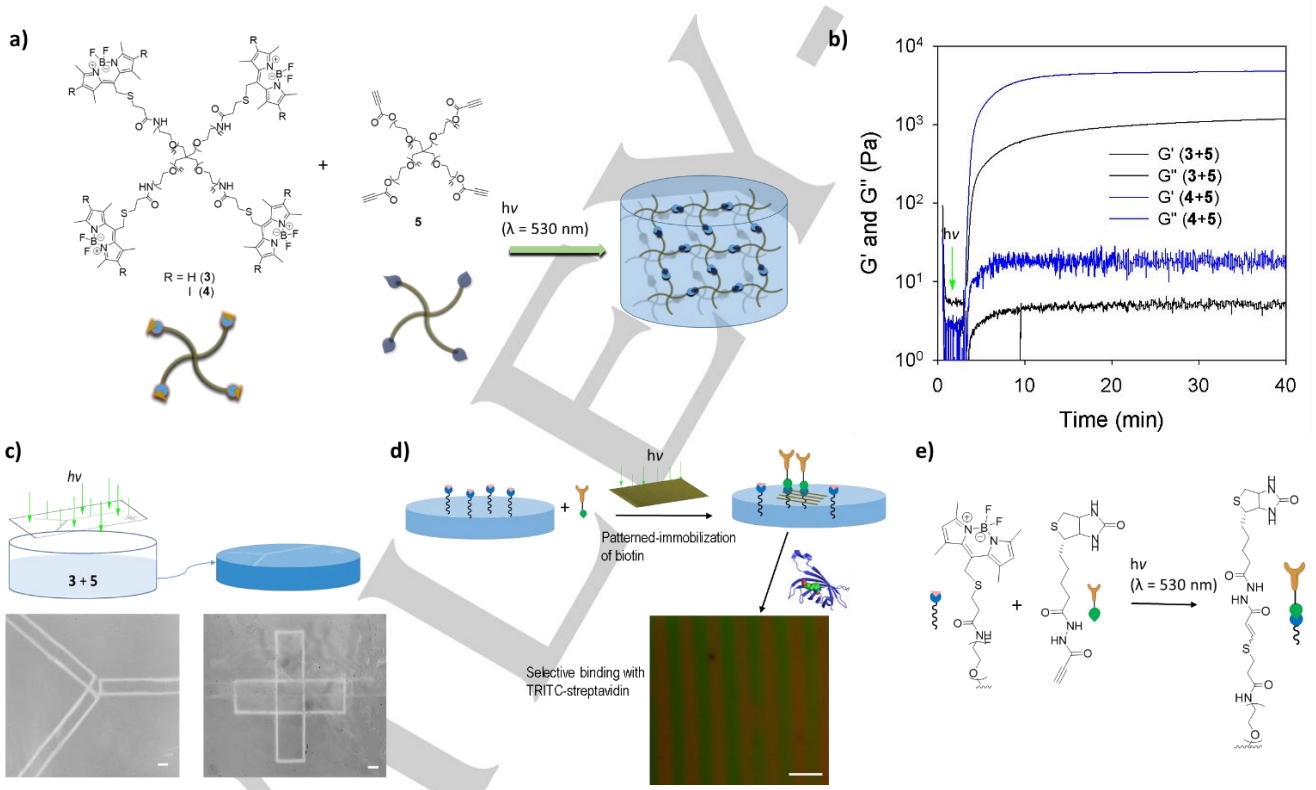

Figure 3. a) Schematic of gelation via green light initiated crosslinking; **b)** kinetics of gelation followed by the change in storage modulus (G') and loss modulus (G") upon irradiation of light (green dashed line) at λ = 530 nm; spatial control of hydrogels properties demonstrated by **c)** fabrication of hydrogels with built-in micro-channels using a brightfield mask (scale bar = 400 µm) and **d)** patterned presentation of TRICT-labelled streptavidin via biotin attachment (the red fluorescence belongs to TRITC-streptavidin while the background green fluorescence is due to thioether BODIPY within the gel, scale bar = 100 µm); **e)** reaction scheme of biotin photo-immobilization.

To demonstrate the utility of our visible light induced chemical ligation in biomaterial science, we synthesised 4-arm poly(ethylene glycol)s (PEGs) with BODIPY thioether end-groups (**3** and **4**) via amide formation and investigated their crosslinking with 4-arm PEG alkyne (**5**) in deionized water under green light illumination (**Figure 3a**). Rheological data show that rapid gelation occurred, as indicated by the evolution of storage modulus, when the polymer-containing solutions were irradiated

with light at λ = 530 nm and I = 30 mW cm^{-2}. Mixture of **3** and **5** displayed an initial rise of storage modulus and thereafter gradual increase to ca. 1000 Pa after 60 min. Similar to the kinetics of small molecule reactions, the gelation rate was faster for PEG having thioether iodinated-BODIPY endgroup (**4**). The crosslinking of **4** and **5** reached completion after 30 min of irradiation, resulting a gel with a *G*' of *ca.* 4200 Pa. Both 4-arm PEGs with thioether BODIPY endgroups were found to have high stability in cell culture conditions – incubation of **3** or **4** at 37 °C for 24 h in PBS solution did not show any change in the UV-vis absorption and NMR spectra. In our previous work on base-catalysed thiol-yne crosslinking, the hydrogels degraded, via hydrolysis of the alkenyl ester linkage, over a period of 1-15 days.[19] We expect that the photo-induced thiol-yne gels would display similar degradation behavior, however the degradation time can be tuned by varying the crosslinking density of the polymer network.

Our studies on small molecules indicate the BODIPY-OH side product can provide competitive absorption of the incident light, which may affect the photochemical process. In general, this effect is minimal at low concentrations or very thin sample,[20] as being designed in small molecule study and rheology set up. To account for light attenuation in a larger sample, we examined the crosslinking of polymer solution (**3**+**5**) having a thickness of 1.2 cm. We found that a solid gel was formed across the thickness investigated (**Figure S34**). In addition, light attenuation after transmitting through the hydrogel sample of this thickness was found to be 60%. In comparison, light at λ_{max} = 470 nm showed 100% attenuation after passing through the same hydrogel sample. This result demonstrates the advantage of utilizing longer wavelength light in materials science such as green light, which provides better medium penetration compared to shorter wavelength blue or UV light.

To highlight the spatiotemporal control over materials properties, we attempted to fabricate a hydrogel with pre-determined architectures using a photomask. Here, a solution of **3** and **5** was covered with a brightfield photomask before being subjected to green light irradiation for 30 min, after which a hydrogels with cross-shape or triple junction microchannels (**Figure 3c**) were formed having width and depth of *ca.* 200 µm ca. 1.2 mm respectively (**Figure S35**). Hydrogels with embedded microchannels are highly valuable for *in vitro* drug discovery model[20] and organ on a chip platforms,[21] however fabrication of well-defined microchannels on hydrogels often relies on printing techniques using cytotoxic materials[22] or UV light-initiated polymerization.[23] Here we demonstrate that hydrogels with built-in microchannels can be formed by simply using an appropriate photomask and a LED light source. Of note, our method may not be able to fabricate channels with nanometer details and resolution compared to soft lithography or direct photo-printing,[24] mostly due to light diffraction during the photo-induced crosslinking process.

The hydrogel network can be further photo-patterned with bioactive molecules, such as biotin. In this demonstration, the hydrogel was first formed using stoichiometric excess of **3** so that the resultant gel contained pendent BODIPY thioether after photo-crosslinking. The gel was then treated with a solution of biotin-propiolate, covered with a chrome photomask (**Figure 4d**) and subjected to green light irradiation for photo-patterned immobilization of biotin (**Figure 4e**) . The gel was then exposed to a solution containing TRITC-labeled streptavidin. The high affinity of biotin towards streptavidin allowed for conjugation of the peptide specifically to the patterned region, and appeared as red fluorescence stripes under a microscope.

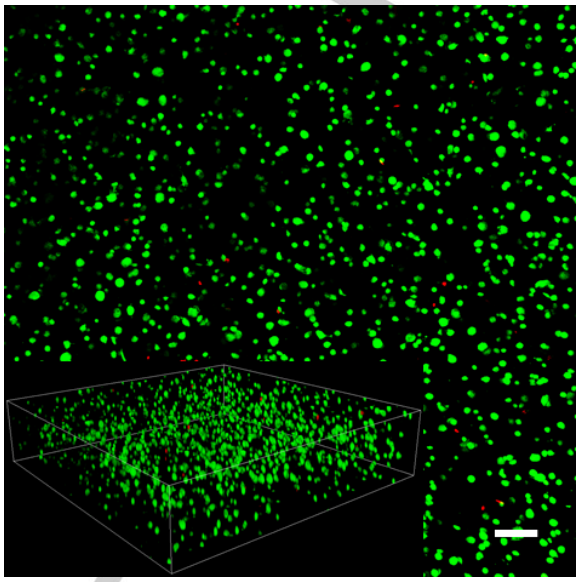

Figure 4. Live/dead staining of hMSC-laden gels 24 h post-encapsulation, (Green = live cells; red = dead cells; scale bar = 100 µm; Z-stack height 300 µm).

Finally, we further tested the suitability of the green light-triggered ligation for three-dimensional primary cell culture studies using human mesenchymal stem cells (hMSCs). In this study, hMSCs were homogenized with a solution containing polymer **4** and **5** before green light-induced crosslinking to form cell-laden hydrogel. The encapsulated hMSCs were then cultured for 24 h and cell viability was assessed by live/dead staining. We observed a very high cell viability (97.9% ± 0.8%), confirming that the green-light induced crosslinking process is non-toxic to hMSCs. Interestingly, although the porpiolate has been reported to be toxic to hMSCs during gelation via base-catalysed thiol-yne crosslinking, the high viability in the photo-induced thiol-yne suggests that the photoligation process reduce the impact of the propiolate group on live hMSCs.[23] Possibly, the low toxicity is due to lower pH used in cell encapsualtion process, as the propiolate is know to be reactive at pH >7.4.

In summary, we demonstrate that BODIPY can be employed as a phototrigger for the thiol-propiolate addition by incorporation to the thioether at *meso*-substitution. The long-wavelenth absorption of the BODIPY moeities allows for activation of the reaction under green light (λ = 530 nm) - by far the longest wavelength employed for additive-free photochemical ligation. As shown here, this new method of visible-light triggered ligation is highly valuable for applications in material manufactering and biomaterials engineering.

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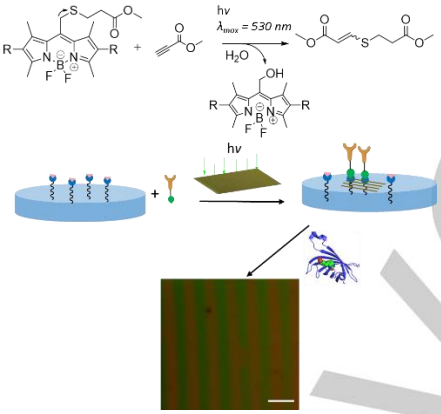
Photochemical ligation between BODIPY thioether and propiolate, triggered by green light, enables formation of hydrogel and photo-patterning of bioactive molecules



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